40. A method for inhibiting the growth of a cancer cell comprising i) contacting the cancer cell with a composition comprising troglitazone and ii) contacting the cancer cell with a chemotherapeutic agent or irradiating the cancer cell, in amounts effective to inhibit growth of the cancer cell.

41. The method of claim 40, wherein the cancer cell is contacted with a chemotherapeutic agent.

42. The method of claim 41, wherein the composition comprises troglitazone and a chemotherapeutic agent.

43. The method of claim 40, wherein the cancer cell is a bone cancer cell.

44. The method of claim 43, wherein the bone cancer cell is an osteosarcoma cell.

45. The method of claim 40, wherein the cancer cell is an ovarian cancer cell.

46. The method of claim 40, wherein the cancer cell is a renal cancer cell.--

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims and Specification

The title of the application has been changed to more accurately describe the claimed invention.

Claims 1, 17-24, 31-32, and 36-38 have been amended in the Amendment submitted herewith Claims 38-46 were added therein. Support for the amendments and added claims can be found in the originally filed claims and in the Specification at least at page 10, lines 18-20; page 42, lines 1-19; page 43, lines 20-page 44, line 16; and page 44, lines 25-27. No new matter

was added by the amendments. Accordingly, claims 1-15, 17-29, and 31-46 are pending. Appendix A contains a copy of the claims in a form Applicants believe is correct.

B. Claims 1-6, 17-29, and 31-38 Are Enabled under 35 U.S.C. § 112, first paragraph

The Action rejected claims 1-6 and 8-38 under 35 U.S.C. § 112, first paragraph as lacking enablement. The Action admits the specification is enabling for methods of inhibiting the growth of a cancer cell or treating cancer based on inhibiting the growth of cancer cell *in vitro* and in nude mice with tumors. However, it alleges the specification does not reasonably provide enablement for these methods *in vivo* in any and all patients, including humans. Applicants respectfully traverse this rejection.

Applicants note that claims 1-8 have been cancelled.

The instant specification satisfies the enablement requirement. Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984). "The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)). The specification shows 1) the effects of troglitazone, rosiglitazone, and pioglitazone—alone and in combination with two separate chemotherapeutic drugs—on a human osteosarcoma cell line (FIG. 5, 6, 8 and 9 and accompanying text); 2) the effects of troglitazone, alone and in combination with two separate chemotherapeutic drugs, on a human renal cell line; and 3) the effects of troglitazone, alone and in combination with a chemotherapeutic drug, on a human ovarian cell line. The specification

also teaches how to administer combination treatments to a variety of cells and several ways to assay cells for inhibition. (Examples 1-4). A person of ordinary skill in the art, at the time the application was filed, equipped with his general knowledge and the specification would be able to practice the claimed invention. That person could experiment with a particular thiazolidinedione and chemotherapeutic drug on a particular cancer cell type to effect the claimed invention of inhibiting the growth of a cancer cell.

The test of enablement is whether the experimentation needed to practice the invention is undue. MPEP § 2164.01 (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). Thus, the need for some experimentation is not fatal to the patentability of an invention. In this case, the experimentation would not be undue because protocols and methods are described in the specification.

Moreover, the disclosure describes how one of skill would obtain *in vivo* data using an animal system. Specification page 39-41. A person of ordinary skill in the art would be able to implement a treatment method involving a thiazolidinedione and a chemotherapeutic drug. Despite the Action's assertions to the contrary, the demonstration of treatment in mice is adequate enablement of the claimed invention; proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana,* 51 F.3d 1560 (Fed. Cir. 1995). *See also Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark (PTO) proceedings.").

The Action cites two references as "demonstrat[ing] the unexpected role of troglitazone and rosiglitazone (BRL 49653) in promoting rather than inhibiting the frequency and size of colon tumors" the *Min* mouse model. However, the Lefebvre *et al.* and Saez *et al.* articles

(collectively referred to as "Lefebvre/Saez articles") are either not relevant to the claimed invention, or, if they are relevant, their relevance is severely compromised in light of recent data. They are not relevant because they are directed to results involving only a thiazolidinedione (TZD) and not a combination therapy; even if they were relevant, their relevance is significantly diminished because there have been clinical trials performed using a TZD, which demonstrates a correlation between efficacy in humans and results obtained from nude mice models in which TZD inhibited the proliferation of cancer cells.

The Lefebvre/Saez articles concern the administration solely of a TZD to a cancer cell while the claimed invention is directed to methods involving contacting a cancer cell with a TZD ***and*** either contacting it also with a chemotherapeutic agent or irradiating it. Furthermore, these articles describe studies in which *Min* mice were used, which is a different system than the nude mice system used in other papers that showed TZD inhibited, not promoted, proliferation. Since these articles are relevant only to treatment with a TZD alone, they are not dispositive of data concerning TZD in combination with a chemotherapeutic or irradiation.

Furthermore, Applicants contend that even if there were data that may have led one of skill in the art to question the effect of TZD on a cancer cell at the time the application was filed, which Applicants have disputed, the disclosure of the present application unequivocally provides information that the effect of TZD on a cancer cell, both with and without a chemotherapeutic or irradiation, is to inhibit proliferation. The data in the Lefebvre/Saez articles and the article cited by Seed that showed inhibition of cancer cells in nude mice (Sarraf *et al.*) involve colorectal carcinoma cells, so cancer cell type is not a distinguishing factor. In the Specification, Applicants reported that TZD inhibits proliferation of renal, ovarian, and osteosarcoma cells *in vitro*. The Declaration of John A. Copland Under 1.132 (Appendix B) and accompanying

exhibits, proves that the combination of a TZD with a chemotherapeutic inhibits the proliferation of a tumor, derived from human renal carcinoma cells, in nude mice. This Declaration provides *in vivo* data concerning the claimed invention. Declaration ¶6 and accompanying Exhibit 2. Thus, the application is enabling for the claimed invention because at the time it was filed, one of skill in the art, armed with the disclosure, would be able to make and use the claimed invention without undue experimentation.

The Action cites Seed to discredit the correlation between rodent and *in vitro* studies to human studies. According to the MPEP, a "rigorous or an invariable exact correlation is not required." MPEP § 2164.03, citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). Despite Seed's statement, which, if interpreted according to the examiner signals the death knell of animal studies, numerous instances supporting this correlation at the time the application was filed. For example, Fujiwara *et al.*(Appendix C) is a paper published in 1994 that demonstrates the anti-proliferative effects of p53 in a nude mouse. In an article by some of the same authors three years later, Roth *et al.*, they show that anti-proliferative effects are observed in humans treated with p53 (Appendix D). Also, the sheer number of scientists using animal models demonstrates the broad acceptance among those skilled in the art of animal models. In 1997, the year before the application was filed, at least 124 articles were published with "nude mice" in the title, according to a search done on the Medline database. Search Results (Appendix E).

As confirmation of this correlation, clinical trials on human patients with TZD, done after the present application was filed, provide evidence of a correlation between animal models that demonstrated an anti-proliferative effect of TZDs on cancer cells and an anti-proliferative effect shown on tumors in humans. In Mueller *et al.* (Appendix F), inhibition of tumor cell

proliferation was observed in humans after treatment with a TZD. Thus, to the extent that in the face of the evidence set forth herein the examiner still maintains that articles about TZD alone are relevant, clinical efficacy in humans with TZD is not only relevant to the patentability of the claimed invention, but also overshadows the Min mouse studies. Thus, at the time the application was filed, one of skill in the art recognized a correlation between cancer studies done in nude mice and results in human treatment, and furthermore, clinical results on TZD after the filing date cast doubt on the Lefebvre/Saez articles and confirm that the application was enabled at the time it was filed.

Furthermore, the Action contends that the treatment of any and all cancers in any patient has is not enabled by the specification. Some of the claims are directed to specific embodiments, such as particular cancers. Dependent claims 11-15 are examples of these embodiments. Applicants contend that these claims are clearly enabled by the specification.

Accordingly, for the above reasons, Applicants contend that the claims are enabled and respectfully request that the rejection be withdrawn.

C. Claims 17, 25, 26, 32, and 36-38 Are Definite

The Action rejects claims 17, 25, 26, 32, and 36-38 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention. Applicants traverse these rejections.

Claims 17 and 25 were rejected as improper Markush claims. Applicants note that Markush language was not employed for these claims as they do not recite "selected from the group consisting of A, B, and C." As such, guidelines regarding Markush-type claims are not applicable to claims 17 and 25. Applicants have employed the term "or," which is acceptable claim language. MPEP 2173.05(i) III ("OR TERMINOLOGY"). "The primary purpose of this

requirement if definiteness of claim language is to ensure that the scope of the claim is clear so the public is informed of the boundaries of what constitutes infringement of the patent." MPEP § 2173, at 2100-163 (7th ed.). Rejected claim 17 recite nitrosourea and an alkylating agent in the alternative, while claim 25 recites intralesional, intramuscular, and regional delivery in the alternative. Applicants contend that the public can ascertain the boundaries of the rejected claims as there is no uncertainty as to what the claims mean. As such, Applicants respectfully request the withdrawal of this rejection.

Claim 26 was rejected for the phrases "suitably dispersed" and "acceptable formulation." The Action asks how a dispersion between a thiazolidinedione and a chemotherapeutic drug is considered to be suitable. Applicants have removed the term "suitably" to clarify the claim. The Action also asks what is to be considered a pharmacologically acceptable or non-acceptable formulation. This is discussed in the Specification at least on pages 47, lines 10-13, which states that "the phrase 'pharmaceutically or pharmacologically acceptable' refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human." Applicants contend that one of ordinary skill in the art, armed with the background knowledge of pharmacology and the teaching of the Specification, would fully understand the scope of the claim. Accordingly Applicants request the withdrawal of this rejection.

The Action rejected claim 32 as being incomplete for omitting essential steps, that is "the entry of a therapeutic polynucleotide into a cancer cell, wherein a therapeutic protein encoded by the therapeutic polynucleotide is expressed in an amount effective to inhibit the growth of said cancer cell." Applicants have amended this claim to clarify further the invention.

Claims 36-38 were rejected also as being incomplete for omitting essential elements. The Action contends that the omitted element is that the administration of troglitazone and a chemotherapeutic drug are effective in inhibiting or reducing cancer cell growth, or delaying or preventing metastases. Applicants have not adopted the Examiner's particular suggestion, but have amended the claims in a manner that further clarifies the claims. Accordingly, the claims are definite and Applicants respectfully request this rejection be withdrawn.

D. The Claims Are Not Anticipated by the Cited References

The Action rejected claims under 35 U.S.C. § 102 (a) as being anticipated by several different references, which will be discussed individually.

1. Claims 1-3, 5-7, 9, 10, and 34 Are Patentable over Mueller *et al.*

The Action rejects claims 1-3, 5-7, 9, 10, and 34 under 35 U.S.C. § 102 (a) over Mueller *et al.* (Mueller). Applicants respectfully traverse this rejection.

In view of the Declaration of John A. Copland under 37 C.F.R. § 1.131 (Appendix G), Applicants contend that Mueller is not a proper prior art reference. Accordingly, Applicants respectfully request this rejection be withdrawn.

2. Claims 1, 4-7, 9, and 10 Are Patentable over Brockman *et al.*

The Action rejects claims 1, 4-7, 9, and 10 under 35 U.S.C. § 102 (a) over Brockman *et al.* (Brockman). Applicants respectfully traverse this rejection.

In view of the Declaration of John A. Copland under 37 C.F.R. § 1.131, Applicants contend that Brockman is not a proper prior art reference. Accordingly, Applicants respectfully request this rejection be withdrawn.

3. Claims 1, 2, 5-10, 16, 17, 24-29, and 33-35 Are Patentable over Elstner *et al.*

The Action rejects claims 1, 2, 5-10, 16, 17, 24-29, and 33-35 under 35 U.S.C. § 102 (a) over Elstner *et al.* (Elstner). Applicants respectfully traverse this rejection.

In view of the Declaration of John A. Copland under 37 C.F.R. § 1.131, Applicants contend that Elstner is not a proper prior art reference. Accordingly, Applicants respectfully request this rejection be withdrawn.

4. Claims 1, 2, 4-10, 16, 17, 24-29, 33 and 35 Are Patentable over Kubota *et al.*

The Action rejects claims 1, 2, 4-10, 16, 17, 24-29, 33 and 35 under 35 U.S.C. § 102 (a) over Kubota *et al.* (Kubota). Applicants respectfully traverse this rejection.

In view of the Declaration of John A. Copland under 37 C.F.R. § 1.131, Applicants contend that Kubota is not a proper prior art reference. Accordingly, Applicants respectfully request this rejection be withdrawn.

E. The Claims Are Non-obvious over the Cited References

The Action rejected claims under 35 U.S.C. § 103 (a) as being rendered obvious by several combinations of references.

1. Claims 1, 9, and 11-15 Are Patentable

The Action rejects claims 1, 9, and 11-15 under 35 U.S.C. § 103 (a) as being unpatentable over Mueller or Brockman or Kubota, in view of Urban and Green's U.S. Patent No. 5,814,647 ('647 patent). Applicants respectfully traverse this rejection.

In view of the Declaration of John A. Copland under 37 C.F.R. § 1.131, Applicants contend that Mueller, Brockman, nor Kubota are proper prior art references. As these references are relied upon to teach the use of a thiazolidinedione compound to inhibit proliferation of cancer cells, the loss of those references renders the remaining reference of Urban and Green insufficient to teach the claimed invention. Patent law requires that the "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP §2142.

Accordingly, Applicants respectfully request this rejection be withdrawn.

2. Claims 1 and 16-24 Are Patentable

The Action rejects claims 1 and 16-24 under 35 U.S.C. § 103 (a) as being unpatentable over Elstner, in view of Medenica *et al.* and Knight *et al.*. Applicants respectfully traverse this rejection.

In view of the Declaration of John A. Copland under 37 C.F.R. § 1.131, Applicants contend that Elstner is not a proper prior art references. As none of the remaining references teaches the use of a thiazolidinedione, as is required by the claims, Applicants contend that a proper *prima facie* obviousness rejection has not been made under MPEP 2142. Applicants respectfully request the withdrawal of this rejection.